

Attorney Docket No.:	DC-0156
Inventors:	DeLeo and Weinstein
Serial No.:	09/857,385
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#### REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been amended. Reconsideration is respectfully requested in light of these amendments and the following remarks.

#### **I. Rejection of Claims Under 35 U.S.C. 103(a)**

The rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Yaksh et al. (U.S. Patent No. 6,180,716; hereafter referred to as the '716 patent) and Heywood et al. (1988), and further in view of *Drug Facts and Comparisons* (1994), has been maintained. The Examiner has suggested that the '716 patent teaches that spinal (intrathecal/epidural) administration of centrally acting agents, such as anti-neoplastics and analgesics, have considerable therapeutic efficacy for treatment of pain, spasticity, central nervous system tumors, and infections, and further that methotrexate is one of these centrally acting agents that is given by intrathecal infusion. The Examiner further suggests that Heywood et al. (1998) teach that rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy while *Drug Facts and Comparisons* (1994) teach administration of methotrexate

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for rheumatoid arthritis by ameliorating symptoms of inflammation (pain, swelling stiffness). As a result, the Examiner suggests it would have *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to administer methotrexate intrathecally for treatment of lower back pain with radiculopathy because motivation is provided by the teaching of the '716 patent (teaching methotrexate intrathecally) and Heywood et al. (1988; teaching rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy) combined with the teaching of *Drug Facts and Comparisons* (1994; teaching that methotrexate is routinely used to treat rheumatoid arthritis to ameliorate symptoms of inflammation). Further, the Examiner suggests that in terms of the dose cited in the claim, *Drug Facts and Comparisons* teaches that administration of methotrexate at a dose of 7.5 mg/week could readily be extrapolated by one of skill to an intrathecal dosage to fit the limitation of an animal. The Examiner then states that an animal weighing 7.5 kg is treated ( $1 \text{ mg/kg} \times 7.5 \text{ mg} = 7.5 \text{ mg}$ ).

Applicants again respectfully disagree with the Examiner's conclusions regarding the combination of cited references, especially as it concerns the issue of dose. In the specification

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as filed, the Examiner points out that the animal mentioned and discussed is a rat. Contrary to the Examiner's suggestion, a rat does not weight 7.5 kg. In fact, a rat typically weighs much less than 1 kg (200-300 g is typical for young adult rats), which is a well-known fact for one of skill in the art. Thus,  $200 \text{ g} \times 1 \text{ mg/kg}$  ( $0.2 \text{ kg} \times 1 \text{ mg/kg} = 0.2 \text{ mg/kg}$ ) as mentioned by the Examiner would be a dose much less than the 7.5 mg that is taught in *Drug Facts and Comparisons*, i.e., only 0.2 mg. Therefore, contrary to the Examiner's suggestions, the dose information provided in that reference is NOT sufficient for one of skill to choose a dose for testing in animals. Giving 7.5 mg to a rat would be equivalent to  $7.5 \text{ mg} \times 1/0.2 \text{ kg}$  or  $37.5 \text{ mg/kg}$ , a dose that would likely be lethal in a rat since the injected  $\text{LD}_{50}$  of methotrexate for a rat is known to be in the range of 6 to 25 mg/kg (see <http://www.medsafe.govt.nz/profs/datasheet/m/Methotrexateinjmayne.htm>). Thus, contrary to the assertions by the Examiner, one of skill would not be able to use the references cited to identify a dose to use as claimed in the instant invention.

However, in order to advance the prosecution and facilitate allowance of the claims, Applicants have amended the claim to recite that the dose of methotrexate of 1 mg/kg is administered every other day for up to 11 days. Support for this amendment to

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the claims can be found at pages 5-6 of the specification as filed where it is taught that the drug was administered to the animals every other day for up to 11 days.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

The claim as amended specifically recites a "1 mg/kg" dose is administered intrathecally "every other day for up to 11 days". As already discussed, nowhere in the references cited by the Examiner is such a dose and dosing frequency taught or suggested. In fact, the only reference that even mentions dosage of methotrexate is limited to oral dosing amounts (see page 1244 of *Drug Facts and Comparisons* 1994). There, the dosage taught is either a single oral dose of 12 mg/week, or a divided oral dose of 2.5 mg at 12 hour intervals for 3 doses given over the course of a week (7.5 mg). Using the rat body weight, this is an oral dose of from 60 mg/kg/week for a rat (12 mg x 1/0.2 kg bw for a

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rat) to 12.5 mg/kg/12 hours (2.5 mg x 1/0.2 kg bw of rat). In the case of methotrexate, a highly toxic drug (see discussion in *Drug Facts and Comparisons* 1994), one of skill in the art would not be able to extrapolate an oral dose range to an intrathecal dose range, especially going higher in dose, which would occur for rats. Thus, a teaching of dose is lacking in the prior art cited, as well as a failure to teach use of methotrexate every other day for up to 11 days. Therefore, the combination of prior art references cited by the Examiner fails to teach or suggest each and every limitation of the claims as filed and cannot make obvious the invention of claim 1.

Moreover, a *prima facie* case of obviousness is established only when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). Thus, an obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). However, in the instant case, the statements made by the Examiner amount to no more than convenient assumptions about what would have been obvious to the skilled

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
artisan at the time of the invention. However, under MPEP \$2144.03, it is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697. See also *In re Thrift*, 298 F.3d 1357, 1364, 63 USPQ2d 2002-2006 (Fed. Cir. 2002) (quoting *Lee*, 277 F.3d at 1344-45, 61 USPQ2d at 1435) (reliance on "common knowledge and common sense" do not fulfill the requirement to provide reasons in support of the findings of obviousness"). As a result, the Examiner's suggestion that it was *prima facie* obvious because all the claimed elements were known in the prior art is improper. Nowhere does this combination of prior art references provide one of skill with any working example of using methotrexate intrathecally for treatment of pain with radiculopathy at any dose, including the dose claimed, or at the frequency as now claimed. Accordingly, this combination of prior art references cannot establish a *prima facie* case of obviousness and withdrawal of this rejection is respectfully requested.

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## II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

  
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